Mobile-enhanced group cognitive behavioral therapy for adolescents with severe mood disorders

PI: Marc J. Weintraub, PhD
UCLA Semel Institute for Neuroscience and Human Behavior

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Study Protocol

Overview of Study

Human Subjects Involvement, Characteristics and Design

Aim 1 involves two sets of human subjects: (1) a focus group (N=8 youth-parent dyads) with individuals who participated in the piloting of the transdiagnostic group treatment for youth at-risk for serious mental illness (SMD); (2) an open trial (N = 12 youth) testing the acceptability of the app-enhanced treatment for youth at high risk for SMD. Additionally, Aim 2 involves human subjects for the RCT (N=60) of the app-enhanced treatment and analysis of the results from this trial. Participants for Aim 1's focus will be recruited from a pool of participants previously enrolled in the pilot testing of our transdiagnostic treatment for youth at-risk for SMD and who consented to being contacted for future research. Participants for Aim 1's open trial and the RCT will be recruited primarily from UCLA's Child and Adolescent Mood Disorders Program (CHAMP). Additionally, flyers will be posted around the UCLA medical campus and within outpatient clinics throughout the hospital. Eligibility criteria is purposely broad to include as many youths at high risk for SMD as possible. Eligibility criteria is as follows:

Inclusion criteria:

1. Meet DSM-5 criteria for at least one past major depressive disorder, persistent depressive disorder, or unspecified bipolar disorder
2. Be 13-17 years old
3. English speaking and able to complete written questionnaires
4. Ability to attend pre-determined group session time(s)
5. Access to a smartphone to engage with the study app (open trial and RCT only)
6. Medication usage is acceptable, but not required

Exclusion criteria:

1. Regular use or current abuse of a psychoactive drug
2. Evidence of behavioral problems that are thought to interfere with group treatment
3. Suicidality that requires more intensive treatment
4. Meeting DSM 5 criteria for bipolar I or II disorder, a psychotic disorder, or significant psychiatric symptoms (e.g., self-injurious behavior) that require more intensive treatment
5. Concurrent participation in cognitive-behavioral therapy
6. Inability to travel to study sessions and assessments

Rationale for study criteria: The high-risk period for severe mood disorders (SMD) ranges from about 13 – 25 years of age, with the peak age of onset between 14-15 years old. To increase cohesion and participant acceptability within a group treatment, we chose to restrict eligibility to a smaller age range. We decided on the ages of 13-17 years old (essentially the high school age period) for a couple reasons. First, it is important for members within the group to be of similar developmental stage and feel comfortable with one another. Having too large of an age-range within a group treatment (e.g., adolescents with young adults) can be problematic as adolescents face different challenges than young adults. Additionally, content of adult discussion can be inappropriate for adolescents. Second, the primary mentor's (Dr. Miklowitz) clinic provides services to children and adolescents, and this clinic serves as one of the primary recruitment sources. Limiting enrollment to individuals with high risk for SMD classifications was based on two main principles. First, individuals with full threshold bipolar disorder or long-standing and unremitting unipolar depression typically require more intensive and disorder-specific treatment. Second, the study questions have largely been tested on individuals with less severe depressive and anxiety disorders. Thus, individuals at high-risk for SMD are uniquely appropriate to address this project's aims. Finally, although speaking English may be a limiting factor for some participants, we have not yet excluded any interested participants from our pilot study based on this criterion. Ensuring that participants share a language with each other is essential for group cohesion and instruction of therapeutic skills. Future grants stemming from this project will include community-based outreach efforts to extend the testing and dissemination of this program to more diverse groups.

Recruitment and screening procedures: *Full details are provided in the Recruitment and Retention Plan.* Participants will be identified using research databases of patients/former research participants who consented to being contacted for future research studies within UCLA's CHAMP. Additionally, participants may learn about the study through flyers placed throughout outpatient mental health clinics or other UCLA Health System

research outreach programs. *I have budgeted in salary support for a research coordinator two days per week throughout Years 1-4 of the award. The research coordinator will screen all interested participants by phone to assess study eligibility, explain the purpose of the study and study procedures, and answer any questions.* For individuals interested and eligible in participating, youth will complete the informed assent process and their parent/guardian will complete the informed consent process (detailed below). In addition to the phone screening of eligibility criteria, an in-person eligibility assessment will be conducted with the PI and research coordinator to assess for DSM/SIPS diagnostic criteria, explain the study procedures in more detail, and answer any questions. Recruitment will be done until there are enough participants to randomize and fill two groups of $n>6$ per group.

Overview of study activities: Aim 1 will consist of focus groups, followed by an iterative app-development process with an interdisciplinary expert panel, and then an open trial of an app-enhanced cognitive-behavioral treatment (CBT). Focus groups will be held in a conference room at the UCLA Semel Institute and last approximately 60 minutes. The open trial will consist of a pre-treatment assessment, nine 90-minute group treatment sessions, and post-treatment session that includes an exit interview. Aims 2 & 3 will consist of a RCT of the app-enhanced CBT, which will compare nine 90-minutes sessions of the group CBT to nine 90-minute sessions of the app-enhanced group CBT. The RCT will also consist of a pre-treatment assessment, a post-treatment assessment, and a 3-month follow-up assessment following the completion of the group. The open trial and the RCT will be held in group therapy rooms at the UCLA Semel Institute. Finally, I will conduct longitudinal and machine learning analyses of data collected throughout the RCT.

Study Procedures, Materials, and Potential Risks

Sources of materials will include information collected from the study screen (i.e., psychiatric mood symptoms, age, contact information, and time availability), qualitative data from the focus groups and open trial, and quantitative data from the open trial and RCT eligibility and study assessments. The study screen will be conducted by phone and the focus groups, open trial, RCT, and eligibility and study assessments will be conducted in person. All information will be collected for the purposes of research and will only be accessible to study staff.

Data collection, management, and protection: The confidentiality of study participants will be protected to the fullest extent. Whenever possible, participant data will be collected electronically using Chorus Innovative Platform (Chorus). In addition to an app-development platform, Chorus also serves as a secure, web-based application to store data. Chorus was developed at UCLA by Dr. Armen Arevian (co-mentor), and is used in a range of IRB-approved studies at UCLA to collect and store data. Locally hosted by UCLA's encrypted servers, Chorus allows for secure electronic collection and management of clinical research data. Upon enrollment, participants will be given a unique identification number to protect all personal and study information. No identifying information will be kept on any study forms. The PI will be responsible for assigning unique study IDs and for maintaining a log that links participant names with their unique study identifier. This log will be password protected, kept separate from study information, and stored in our study network folder (which is backed up nightly). Only IRB approved study staff will have access to any research or personally identifying data. Consent forms will be stored in a separate locked filing cabinet within the PI's office. *Given the provision of information in a group setting, group members will be asked to complete a statement of confidentiality wherein participants are asked not to discuss specific information pertinent to any group member with anyone.* All digital audio recordings for focus groups, therapy sessions, and study assessment will be immediately uploaded onto the secure study network folder and the file will be deleted from the recorder. All audio files will be password protected and only accessible to study staff.

Potential Risks: The risks involved in the study are minimal. Participants may experience some discomfort by talking about their symptoms or by some of the topics brought up during the groups/assessments; however, they may choose not to answer questions that are distressing. Participants may also experience discomfort talking in a group setting or being audio-recorded. Confidentiality will be detailed on the consent form and discussed in person so that participants are fully informed of their right to request information and to withdraw from the study at any time without impacting their care. We will also discuss the importance of maintaining other participants' confidentiality at the beginning of each focus group and treatment group cohort. The risk of psychiatric consequences is minimal; however, there is always the potential for worsening of psychiatric symptoms or distress. If any participant expresses considerable emotional and psychological distress, the

study PI (licensed clinical psychologist) will immediately inform the co-investigators, Drs. Miklowitz (licensed clinical psychologist) and Drs. Zima and Arevian (board-certified psychiatrists). Collectively, they will ensure that any participant with elevated distress are safe and receive immediate care. Additionally, referrals for additional psychiatric care will be made as necessary. The study PI's contact information will be provided on each of the consent forms for participants to access if they have additional questions or concerns.

The assessment battery has been designed to minimize participant burden but to cover the domains and constructs relevant to the study's hypotheses. Participants may at times feel inconvenienced by the time required to complete the questionnaires. Participants will be compensated for completing each interview/assessment battery at the 3-month intervals, and research interviews will be scheduled at the times (for example, after school) most convenient for the family. In the primary mentor's prior trials, rates of compliance with in-person follow-up interviews have ranged from 78% - 88% over 2 years (Miklowitz & Chung, 2016).

Participants may at times experience sadness or discomfort when discussing family issues, personal problems, or psychiatric symptoms, but no more than they would if they took part in psychotherapy or pharmacotherapy sessions in the community. Discussing psychiatric problems may at times be upsetting to the adolescent. If these reactions occur, the research staff, all of whom are well-trained and supervised by the PI (a licensed psychologist), will offer the participants emotional support and validation. Participants will also be informed that they can receive and follow-up on referrals for counseling outside of the study at any time.

The adolescents recruited for this study will meet criteria for a mood disorder and deemed at risk for a severe mood disorder. There is no reason to suspect that adverse events related to the illness (e.g., hospitalizations) will be higher if the adolescent receives treatment in the study instead of in a community treatment setting. In fact, because of the psychosocial protocols administered in this study, the increased availability of between-session communication with study staff, rates of adverse events may be lower than if patients were treated in the community. Nonetheless, we will track all adverse events – whether study related or not - using an Adverse Events Form previously developed for this age group and used in the primary mentor's family therapy trials.

ADEQUACY OF PROTECTION AGAINST RISKS

Training of Staff

All research staff proposed for the study have received human research ethics and HIPAA training. They will be trained in the study's recruitment and informed consent procedures before collecting any data for this study. The PI and primary mentor will develop a study procedures manual that clarifies how to explain the study to participants and parents and address questions about random assignment and other study-related matters. Training will require that study staff read through and discuss the manual and participate in role-plays of the recruitment and informed consent process (for example, how to determine if the proband and parents fully understand the protocol before signing informed consent or assent documents). The PI will supervise the recruitment of study participants, and will meet regularly with the primary mentor to review recruitment progress.

Referral to the Program

Recruitment will start when an adolescent or their parent self-refers to the project or is referred by a treating physician or psychotherapist. When study candidates are referred by a mental health professional, this professional will give the participants a copy of an IRB-approved study flyer explaining the purposes and design of the study. The treating clinician can offer to contact the research team if the adolescent and at least one parent signs a HIPAA Authorization Form releasing their protected health information (names, diagnosis, ages, address, and telephone number) to the research team. This release will enable the team to contact the participants to determine their eligibility. A copy of the signed authorization form will be provided to the participants and placed in their medical chart. Alternatively, many families prefer to make the initial contact themselves rather than have their physician make the contact.

Telephone Screening, Informed Consent and Screening Visit

After referral to the program, the project coordinator will initiate a telephone interview of one or both parents of the adolescent. The coordinator will ask the parent to clarify the adolescent's reasons for referral to the program. If the adolescent and parents are interested and the adolescent appears eligible, they are invited to conduct a baseline eligibility assessment.

The initial baseline visit is intended for the adolescent and his or her primary caregiver(s). During this visit, we will obtain information on the presence of mood symptoms in the past month, past and current diagnoses and treatment for a psychiatric disorder and current medications and psychosocial treatments (if any). The project coordinator will explain the study protocol, answers all questions, and conducts the a semi-structured interview to determine eligibility. If the candidate is eligible, and the candidate and family wish to proceed, the project coordinator explains the written consent/assent documents to the parent(s) and adolescent. The coordinator will explain that, if the adolescent meets eligibility criteria the study offers treatment through a randomly assigned protocol involving either family psychoeducation and skills training or family psychoeducation and supportive individual treatment.

Once the parents and youth have signed the consent and assent forms, a trained research diagnostician (independent evaluator) will administer the Structured Clinical Interview for DSM-5 (SCID-5 Research Version; First et al., 2015). This interview and scale ratings are conducted separately with the adolescent and at least one parent, with the adolescent's diagnostic consensus ratings based on both reports. When necessary, these interviews can be spread over two appointments.

In the event that there are unanswered questions about eligibility (e.g., whether the adolescent has regularly abused substances in the past 6 months), additional interviews with the adolescent and parent may be required. After reviewing the baseline assessments, the study staff and PI will meet to determine eligibility. Feedback will be provided to the family regardless of whether the adolescent meets eligibility criteria for the study. All subjects will receive copies of the signed consent or assent documents, HIPAA authorization forms and 'The Experimental Subject's Bill of Rights'.

Informed Consent and Assent

Upon meeting study criteria, youth participants will be assented and their parent/guardian will be consented in person. Prior to consent, the PI will explain study procedures in detail, discuss potential risks and benefits of participation, remind them that the study is voluntary and their choice to participate will not impact the care they receive. They will be informed that they can choose to withdraw freely and may also choose not to answer any questions. They will get the PI's contact information as well as UCLA's IRB contact information if they have additional questions or concerns. The PI will assess patients' understanding of the study and study procedures and will provide them with a copy of their signed consent form to keep. Study consent forms will be kept separately from study data and will be locked in a filing cabinet within the PI's research office. We will submit for approval of all study procedures and protocol to the UCLA IRB prior to initiating any study activity.

Limits to Confidentiality

This study proposes to recruit a relatively young (ages 13-17) sample. If the researchers have reasonable cause to believe that child abuse or neglect is occurring, or there are circumstances which might result in child abuse or neglect, they will comply with California state laws by filing a child abuse report with the Department of Child and Family Services. If the research staff believe that a participant is at risk of harming someone else, they are required to take necessary actions. These actions include notifying the parent of the participant's intentions, notifying others who might be affected (i.e., intended victims), or notifying the police or the Department of Child Services. In these cases, the research staff will be unable to preserve the participant's confidentiality. These limits to confidentiality will be spelled out in the participants' consent and assent forms. We will notify parents if we learn that an adolescent participant is actively abusing alcohol or drugs in a way that is life-threatening or otherwise a danger to him- or herself or others. If an adolescent participant has experimented with a drug or alcohol on a single occasion, notifying the parents may not be indicated. Nonetheless, it will be necessary to monitor this behavior in family or individual support sessions. If we disclose these behaviors to parents, we will meet with the family to help resolve family conflicts and introduce preventative measures. Additional counseling sessions beyond the required number will be tabulated and included as covariates in the treatment/outcome analyses.

Protections Against Risk

Data safety will be maintained to the most rigorous standards as detailed above. Survey responses will be entered into Chorus. Electronic and audio data will be stored within the UCLA Health System's encrypted firewall, will be password protected, and protected by anti-virus software. Any hard copies of participants' data will only contain a unique study ID and stored in a locked filing cabinet within the PI's office. All study codes (including a link between participant names and identifying information) will be kept in a password-protected electronic file on a secure server. Password access will be limited to the PI and to any individuals that are IRB

approved for this study. All study links between participant IDs, names, and identifying information will be destroyed when the study has ended. Approval of all study documents will go through UCLA's IRB.

Data Monitoring
Study recruitment, enrollment, and retention will be reviewed by the PI and research coordinator weekly and by the primary mentor (Dr. Miklowitz) and co-mentors (Drs. Zima and Sugar) monthly. Additionally, twice annually, the scientific advisory committee consisting of the PI, his mentors, and the collaborator and consultants (Drs. Arevian, Granholm, and Ehrenreich-May) will review study recruitment, enrollment, and retention at one of the regularly planned meetings with this team. Informed consents and randomization will also be reviewed weekly by the PI and study coordinator and monthly by the PI's mentors for the purposes of quality control. The research coordinator will report any difficulties in recruitment, enrollment, mobile application (app) implementation (e.g., technological bugs), or other study related difficulties during weekly team meetings.

The focus groups, open trial, and RCT involve data collection via clinician-rated interview/assessment, participant self-report on the mobile app, and speech samples collected via a voicemail-like voice journal. All participant data will be kept confidential and accessible only to approved study staff. Clinician-rated interviews/assessments will not contain any personally identifying information and will be secured in a locked cabinet in the PI's office. Participants' self-report data and speech samples will be collected using the Chorus Innovative Platform and stored on its server, a secure and encrypted server housed within UCLA that has been approved by the university's IRB to house personal health information on multiple research projects within the hospital. These data will only be accessible to study staff approved by the UCLA IRB. The clinical psychology postdoc will review the data collected on the mobile app and the speech samples daily and report any clinically concerning information (e.g., suicidal ideation/intent) immediately to the PI. The PI will then consult with the mentorship team and take any needed action in accordance with California state law and best clinical practice (see Protection of Human Subjects). The PI and his mentors will serve as the data safety and monitoring board to review study participant safety, study progress, and study-related events (including adverse events). As needed, an action plan will be established to ensure continued progress and success in both study and training goals.

Vulnerable Subjects
This study involves children (i.e., individuals under the age of 18) who are at high risk for SMD. As the high-risk period for SMD begins in early adolescents, typically around 13 years of age, the project focuses on adolescent subjects. Given that the risks involved in the assessment measures and treatment for this study are minimal, and that the data derived are anticipated to be extremely useful for improving our understanding of how a mobile application can improve patient compliance to treatment, we believe that the involvement of these patients with elevated psychiatric symptoms is justifiable.

Addressing Clinical Emergencies
Participants and their family members will be instructed to notify their assigned clinician and the treating psychiatrist (if applicable) if they observe sudden deteriorations in the mood or behavior of the adolescent at home or in the school setting. Study participants who are judged to be in need of psychiatric (medication) treatment, and who are not currently receiving such treatment, will be referred as clinically indicated. Participants will have access to the inpatient units at UCLA's hospital.

When clinically appropriate (e.g., worsening mood symptoms or intensifying suicidal ideation), project clinicians will accompany the participant to the emergency department of the relevant hospital and stay with the individual until they have been seen by the inpatient admitting team. If the participant lives far away and the contact is made by phone, clinicians will instruct the proband and as to how to access the nearest hospital emergency room. The clinicians will facilitate communication between the family and the hospital. In all cases, they will re-contact the family within 24 hours to be sure that contact has been made with the appropriate care provider.

Special precautions will be undertaken to prevent the onset of suicidal crises in all participants. First, we will learn of new onsets of suicidal ideation or new attempts because we will have regular contact with participants and their parents for at least the 3-month protocol in the open trial and the 6-month study protocol in the RCT. Information about suicide will be obtained by the assessment clinician at each of the study assessments. Additionally, clinicians will inquire about suicidal ideation during the check-out portion of each treatment

session. Suicidal ideation may also emerge from the participant's weekly responses to the mobile app, which contain questionnaires about mood and suicidality. Independent evaluators will contact the study PI if there is an increase in suicidal ideation or self-harming behavior so that crisis counseling can be introduced or emergency services can be commenced. When a participant endorses suicidal thoughts, the clinician will conduct a thorough lethality and safety assessment and arrange hospitalization if necessary.

If the suicide risk is deemed low, the project clinician will intervene to prevent deterioration. Prevention will include additional meetings with the participant following each treatment sessions. These meetings will involve some or all of the following: (a) conducting chain analyses to assess the precipitants and consequences of suicidal thoughts or actions, (b) developing a suicide prevention contract (i.e., identifying triggers for suicidal thoughts; clarifying the steps by which parents can get in touch with the psychiatrist or therapist and what to do if they are unavailable), (c) enhancing family members' expressions of support, concern, and compassion; and (d) family problem-solving to eliminate triggers of the proband's suicidal thoughts and prevent their worsening.

Availability of Other Ancillary Treatments

Participants may require out-of-protocol emergency services such as hospitalization or other psychosocial programs. These participants will be retained in the protocol whenever possible. A participant who needs to be hospitalized (e.g., for suicidality) will be reentered into the protocol after hospital discharge if the participant and family agree to continue. Participants will not be withdrawn if they seek ancillary psychosocial treatments outside of the study. We recognize that the availability of adjunctive non-protocol treatments could statistically confound our results, especially if they occur in one treatment condition more than another. This potential threat to internal validity must be balanced against the clinical needs of the adolescent participant, which may not be met by study protocol interventions. As indicated, we will record each participant's non-protocol treatments (e.g., medications received, frequency and type of extra psychotherapy sessions) using a *Treatment Utilization Form*. We will examine in the data analyses whether the adolescents in the two treatment conditions differ in the intensity (e.g., number of non-protocol sessions), costs, or duration of ancillary services or crisis sessions. We will then use these variables as covariates when evaluating the effects of treatment condition on the teen's symptomatic, functional, or family outcome variables. In the primary mentor's prior studies in mood disorders (e.g., Miklowitz et al., 2013), youth at high-risk for bipolar disorder in FFT and Enhanced Care did not differ on the frequency of variables such as undertaking ancillary therapies, emergency room visits, school counseling, or hospitalizations.

Circumstances That May Require Study Withdrawal

Noncompliance. Participants will be withdrawn from the protocol if they are noncompliant with the study procedures (for example, miss 4 consecutive treatment sessions without calling ahead; refuse to participate in follow-up interviews). The circumstances that may require administrative withdrawal will be spelled out in the consent forms.

Substance or alcohol abuse. Youth who meet current DSM-5 substance or alcohol abuse or dependence criteria will not be included. If the adolescent shows evidence of regular substance or alcohol use after randomization (during the study protocol) and/or develops a DSM-5 substance/alcohol abuse or dependence disorder, we will retain him or her in the study protocol for as long as possible and work toward abstinence. In most cases we will make referrals for adjunctive chemical dependency treatment. We will make this determination on a case-by-case basis as medically or ethically appropriate. Referrals can include age-appropriate modified 12-step programs with psychiatric oversight, drug rehabilitation facilities, and various forms of individual treatment (i.e., motivational enhancement, cognitive-behavior therapy). Study staff members will follow-up to assure that the youth and family have pursued adjunctive treatment. Adjunctive chemical dependency treatment will not preclude continued participation in the study protocol.

In cases where the adolescent participant continues to use substances and must be discontinued from the protocol, we will refer the proband/family to the appropriate substance abuse treatment clinic. Continuation in the study under these circumstances would not be clinically indicated and would also contaminate analyses of treatment/outcome effects given that the majority of patients in the study are likely to be non-substance abusing. Thus, our policies reflect our study's inclusion/exclusion criteria: (1) excluding participants who have active and severe chemical dependency or abuse, and (2) including those who have experimented with drugs or alcohol but have not become persistent users, and (3) introducing early interventions for substance abuse whenever appropriate.

Significant symptomatic or functional deterioration. If a participant or family member endorses significant symptomatic or functional deterioration at any point throughout the study protocol or if study staff witness significant deterioration, the participant will be encouraged to seek services with ancillary psychosocial and/or psychopharmacological therapy. Study staff will make every effort to continue to include the participant in the study protocol and participants will be continued in the treatment if they continue to consent to treatment, can tolerate the study protocol, and are not a disturbance to the group setting of the treatment. In cases where the patient requires hospitalization, can no longer tolerate the study protocol, or become a disturbance to the group, the participant will be withdrawn from the study.

Participants will have been informed of these rules during the recruitment phase of the study, both through information given orally and via our informed consent procedures. We will make clear that discontinuing participation in the study will in no way jeopardize their access to other treatments provide by outpatient or inpatient services at the study site. Whenever possible, we will continue to follow these adolescents/YAs using the research outcome battery so that they can be included in intent-to-treat analyses.

Reporting Adverse Events
The PI (Dr. Weintraub) will be responsible for monitoring safety throughout the study and complying with reporting requirements. The PI will assume responsibility for reporting all adverse events to UCLA's Institutional Review Board (IRB) and/or federal agency, as necessary. The PI will report to NIH on an annual basis a summary of participants' sociodemographic characteristics, expected and actual accrual rates, retention rates in each treatment condition, quality assurance, and regulatory issues that arise. A summary of adverse events and protocol changes will also be included. Adverse events are defined as unexpected, potentially harmful consequences to study participants that may be related to study procedures. Study personnel will report any complications that are considered to be study related immediately (within 24 hours) to the PI. Serious adverse events will be reported to the primary mentors within 24 hours and to NIH and UCLA IRB within 48 hours; non-serious adverse events will be reported to these groups within 5 days. All adverse events will be submitted on an annual basis for review by the PHRC. Study staff will also be required to undergo NIH training in the conduct of research with human subjects prior to engaging in any research activities.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO RESEARCH PARTICIPANTS AND OTHERS

Benefits to the Participants and Knowledge Gained
The benefits to participants are moderate to high. Participants will have the opportunity to discuss ongoing concerns related to their psychiatric symptoms, including difficulties managing their mood and unusual experiences. Specifically, participants in the groups will have the opportunity to discuss experiences that other peers may not relate to and may even stigmatize. Discussing these experiences and concerns within a group setting provides youth with valuable peer support. This shared experience can help foster self-acceptance, self-efficacy, and emotional validation. Participants engaging in the open trial or the RCT will also be learning evidence-based cognitive-behavioral skills that have been shown to be efficacious for similarly aged youth. Thus, getting exposure to these skills can be provide the participants with useful methods of managing stress and coping with their psychiatric symptoms. Additionally, the participants who receive the app-enhanced treatment will have the luxury of readily-accessible psychoeducation and CBT skills on their smartphone. Quick and easy access to psychoeducation and therapeutic skills provides these participants with a beneficial resource that is not commonly available.

Any potential risks to participants, which we believe are minimal, are reasonable and outweighed by these moderate to high potential benefits.

IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Knowledge Gained
The scientific significant of this study is detailed in the Research Strategy. SMD affects a significant proportion of the population, creating a significant emotional and financial burden on society. Finding ways to intervene effectively in the early stages of SMD is critical. While there are current interventions for the early stages of SMD (most notably CBT), their efficacy is inconsistent and with small effect sizes overall. One proposed reason for the small effect sizes is the low rates of patient compliance to treatment. CBT, as a skills-based

treatment, is based on the premise that participants need to practice the skills in order to improve. Since participants commonly forget to do the skills, lose their homework assignments, or feel unmotivated to complete the skills, it challenges treatment developers to improve the current treatments and address these barriers to patient compliance. ***We propose using a mobile app to improve patient compliance for youth at risk for SMD***. A mobile app can remind participants of skills they need to practice, provide the psychoeducation and skill-practice within the app, and provide contingencies that reward and increase motivation for skill-practice. Additionally, the large amounts of data that a mobile app collects allows for advanced statistical techniques, such as machine learning, to be applied. These efforts can provide a wide range of benefits to youth at risk for SMD and clinical science more broadly. Improving patient compliance can improve treatment outcomes, which reduces burdens on families who face these psychiatric challenges and society at-large who faces this emotional and financial burden. Additionally, through use of machine learning, we can better determine who will and who is benefitting from a skills-based treatment, like CBT. This prediction can help us better tailor treatment recommendations for patients and determine which patients will or will not benefit from a particular type of treatment.

STATISICAL DESIGN AND POWER

Power calculations

For this pilot RCT, we plan to randomize 60 participants to the randomized controlled-trial of the mobile-enhanced treatment. The two treatment groups will be randomized in a 1:1 ratio. Based on pilot trials of this treatment group as well as my primary mentor's (Dr. Miklowitz's) previous work with interventions for adolescents at high risk for SMI, we anticipate no more than 15-20% dropout by the end of the six-month study. Thus, we expect a final sample size of about 50 with full follow-up (25 in each treatment condition) across 3 assessment time-points (baseline, post-treatment, and three-month follow-up). Actual power will be higher as our general linear mixed modeling allows inclusion of data from subjects with partial data. Additionally, data collected via the mobile application (app) should greatly increase the number of measurements.

The power calculation assumes a two-sided significance level, α=.05, and a within-subject correlation of r=.5 between repeated measures. Under these calculations, for outcomes measures at the three primary assessment time-points, we have 80% power to detect an overall group by time interaction corresponding to a differential treatment effect across the two study arms with an effect size of f=.30, just above the above Cohen's threshold for a medium effect (f=.25). Thus, recruiting 60 participants will provide ample data for this pilot RCT in order for us to determine initial clinical meaningfulness for the larger grant application to follow this study. *However, in accordance with NIMH guidance on the role of pilot RCTs (see: https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-18-706.html), this study does not propose to formally assess clinical efficacy or estimates of effect size, due to the unreliability of estimates and limited statistical power yielded from pilot studies.*

Statistical analyses

Aim 1 – App acceptability:

- Open trial acceptability: Following the open-trial, we will score participants' rating of app acceptability and treatment satisfaction and burden. We expect high ratings of acceptability (scores>4/5) for the treatment and the app. We will also calculate participant adherence via the extent of weekly practice and percentage of weekly skills practiced. We expect the percentage of weekly skills practiced to be greater than our pilot study as well as the average homework adherence in the literature (>50%).

Aim 2 – Pilot RCT of App-UP:

- Primary Analyses: Treatment conditions will be compared using a general linear mixed modeling (GLMM) approach for the weekly measurements of treatment adherence (both self-report and clinician rated measures) using IBM SPSS software. Time will be based on the standard interval assessments of the study – the baseline, post-treatment, and follow-up assessment). Time, treatment condition, and their interaction will be the primary predictors (controlling for any significant covariates).

The remaining measures for treatment adherence (i.e., Homework Compliance Scale and Psychosocial Compliance Scale), as well as measures for app acceptability (i.e., Subjective App Usability Scale) and treatment acceptability (i.e., Subjective Treatment Acceptability) will be collected at the post-treatment assessment. Maintenance of treatment adherence will also be collected at the 3-month follow-up assessment. Treatments will be compared on these outcome measures using one-way analysis of variance (ANOVA).

- Secondary analyses: Treatment conditions will be compared using a general linear mixed modeling (GLMM) approach for secondary outcome variables (i.e., psychiatric functioning and psychosocial functioning) using IBM SPSS software. Time will be based on the standard interval assessments of the study – the baseline, post-treatment, and follow-up assessment). Time, treatment condition, and their interaction will be the primary predictors (controlling for any significant covariates). Psychiatric symptoms, psychosocial functioning, and emotion regulation (measured continuously) will be the outcome variables for these analyses.

  We will also test a mediation analysis, with average participant adherence (measured throughout the study) as the mediator between treatment conditions and the secondary outcome variables. This will be done in two sets of analyses using the SPSS Process macros, which is a statistical package within SPSS that runs bootstrapped mediation analyses. First, the effect of treatment condition, mediated by average treatment adherence, on post-treatment psychiatric and psychosocial functioning will be examined. Second, the effect of treatment condition, mediated by average treatment adherence, on 3-month follow-up psychiatric and psychosocial functioning will be examined.

- Exploratory analyses*:* Two exploratory analyses will be examined. We will make use of the app's big data collection to begin to elucidate the app's effect on participant adherence and clinical outcomes.

  1. Using functional data analytic techniques, the uptake of that app will be examined. First, each of the components of participant adherence (skill-practice, symptom monitoring, and review of session content) will be examined to determine the functional pattern of participant adherence over time. This analysis will examine the trajectories of each component of participant adherence over the study to examine their function (i.e., increasing, decreasing, stable over time). Additionally, this analysis will determine which component of participant adherence had the highest frequency of practice.

  2. The frequency and duration of app use will be mapped across the study to determine how often and for how long participants engaged with the app. Additionally, the frequency and duration of app use will be moderated with time of reward reinforcement to determine if the use of the app was affected by the reward structures (e.g., leveling up, receipt of an emoji) within the app.